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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,682	SU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-16 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-16 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment to Non-final rejection filed on February 18, 2009 is acknowledged. Claims 17-31 have been cancelled, and new claims 32-35 have been added. Claims 1-8, 10-16 and 32-35 are pending in this application, and examined on the merits in this office action.

Withdrawn Objection

1. Objection to claim 1 is hereby withdrawn in view of Applicant's amendment to the claim.

Maintained and Revised Rejection

35 U.S.C. 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. (Necessitated by Amendment) Claims 1, 4-5, 7-8, 10-14, 16 and 35 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chan EY (US Patent No. 6,210,896).

4. Chan EY teaches methods and products for analyzing polymers, and the use of molecular motors to move polymers with respect to a station such that specific signals

arise from the interaction between the polymer and an agent at the station (see abstract). The reference teaches the method for analyzing polymers based on the ability to examine each unit of a polymer individually, and by examining each unit individually the type of unit and the position of the unit on the backbone of the polymer can be identified (see column 2, lines 32-38). Furthermore, the reference teaches that one aspect of linear analysis techniques involves the movement of the polymer past a station in such a manner as to cause a signal that provides information about the polymer to rise (see column 2, lines 52-55). Furthermore, the reference teaches that a method for analyzing a polymer includes the steps of exposing a plurality of individual units of a polymer to an agent selected from the group consisting of an electromagnetic radiation source, a quenching source, and a fluorescence excitation source causing the molecular motor to move the polymer relative to the agent, and detecting signals resulting from an interaction between the units of the polymer and the agent (see column 2, lines 60-67 and column 26). Furthermore, the reference discloses that another preferred method of analysis involves the use of radioactively labeled polymers (see column 27, lines 9-10) and the analysis of the radiolabeled polymers is identical to other means of generating signals (see column 27, lines 47-48). The reference teaches that in one embodiment, the polymer dependent impulses measured is an electromagnetic radiation signal generated, and the units are detected at the signal generation station by measuring light emission at the station, the station can be a nanochannel (see column 6, lines 5-9). The reference further teaches a method for determining the order of units of a polymer of linked units, the method steps includes 1)

moving the polymer linearly relative to a station using a molecular motor, 2) measuring a polymer dependent impulse generated as each of two individual units, each giving rise to a characteristic signal, pass by the station, 3) repeat steps 1 and 2, and 4) determining the order of at least the two individual units based upon the information obtained from said plurality of similar polymer (see column 5, lines 54-63). The reference further teaches that the polymer may be any type of polymer of linked units…nucleic acid or peptide (see column 3, lines 27-32). This reads on claims 1, 5, 7-8, 11-14. The reference further teaches that the labeled polymer is moved linearly relative to a station to produce a characteristic polymer dependent impulse generated as each of the two unit labels passes by the station, and further comprising the step of determining the distance between the polymer dependent impulses as an indication of the distance between the two unit labels (see column 4, lines 35-41). This reads on claims 1, 4, 7-8 and 16. Furthermore, the reference teaches that the method is a method for determining the proximity of two unit labels of the polymer wherein the proximity of the two unit labels is the signature of said polymer dependent impulses, the identity of each unit label being indicative of the identity of at least one unit of the polymer, wherein the labeled polymer is moved relative to a station to expose the two unit labels to the station to expose the two unit labels to the station to produce a characteristic polymer dependent impulse arising from a detectable physical change in the unit label or the station, and further comprising the step of measuring the amount of time elapsed between detecting each characteristic polymer dependent impulse, the amount of time elapsed being indicative of the proximity of the two unit labels (see

column 4, lines 42-54). This reads on claim 10. The reference discloses that sequence of polypeptide is determined by comparing the relative mass difference between fragments with the known masses of the amino acid residues (see column 2, lines 8-21). This reads on claim 4. Furthermore, the reference discloses that the ability to determine the distance between two units is important for determining how many units, if any, are between the two units of interest and the sequence of units serves as a blueprint for a known polymer (see column 13, lines 25-32). The reference teaches that the method is performed on a plurality of polymers, simultaneously (see column 4, lines 8-9). The reference teaches that multiple polymers can be analyzed simultaneously by causing more than one polymer to move relative to respective signal station on respective molecular motors (see column 8, lines 64-66). Furthermore, the reference teaches that FRET analysis can be performed on a single molecule in solution or as parallel reactions on a solid planar medium, or in different solutions, such as in multi-well dishes (see column 9, lines 29-32). Furthermore, the reference discloses analysis of labeled peptide analyzed by nanochannel FRET sequencing. The sequence-specific FRET information arising from each fragment is sorted into one of two complementary strand groups, sorting allows population analysis to determine the positions of all the desired bases, and to thus generate sequence information from the sorted data (see column 21, lines 19-26). Additionally, Example 6 of the reference teaches that polymer is pulled closer to tip using dielectric forces created by applying an AC field to electrode and waveguide, i.e., metal layers, in addition to the DC field applied across wires. The AC field applied capacitively with respect to the DC field generates an inhomogeneous

field in nanochannel (see column 36, lines 14-19), meeting the limitation of inner surface of the nanopores coated with a semiconductor material. As evidenced by the instant specification, "the sensor layers may comprise semiconductor material including, but not limited to, silicon, silicon dioxide, silicon nitride, germanium, gallinium arsenide, and/or metal-based compositions such as metals or metal oxides (see paragraph [0078] of instant specification US 2005/0282229 A1). In regards to claim 35, the instant specification does not define what a “sub-nanometer scale" is. Further, since the proteins, polypeptides or peptides are passing though nonochannels, it would inherently have nanometer scales. Furthermore, claim 35 does not further limit the active method steps of claim 1. Therefore, the reference meets the limitations of claims 1, 4-5, 7-8, 10-14, 16 and 35.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 4-5, 7-8, 10-14, 16 and 35 remain rejected under 35 U.S.C. 102(e) as being anticipated by Chan EY (US Patent No. 6,355,420).

6. Chan EY teaches methods and products for analyzing polymers, and methods for determining various other structural properties of the polymers (see abstract). The reference further teaches that the method for analyzing polymers according to the invention is based on the ability to examine each unit of a polymer individually. By

examining each unit individually, the type of unit and the position of the unit on the backbone of the polymer can be identified (see column 6, lines 48-50). Further, an individual unit of the single polymer in one aspect is caused to interact with an agent such that a change, e.g., energy transfer or quenching occurs and produces a signal (see column 7, lines 1-4), and the signal is indicative of the identity of the unit (see column 7, lines 4-5). Furthermore, the reference teaches that the polymer may be any type of polymer known in the art…is selected from the group consisting of a nucleic acid and a protein (see column 8, lines 49-51). The reference discloses that the units of the polymer which interact with the agent to produce a signal are labeled and the units may be intrinsically or extrinsically labeled, and the plurality of individual units of the polymer are exposed to at least two stations positioned in distinct regions of the channel, wherein the interaction between the units of the polymer and two stations produce at least two signals (see column 8, lines 53-67). The reference teaches that the method includes the steps of transiently moving the individual unit of the polymer relative to a station, the identity of the individual unit being unknown, detecting a signal arising from a detectable physical change in the unit or the station, and distinguishing said signal from signals arising from exposure of adjacent signal generating units of the polymer to the station as an individual unit (see column 10, lines 1-7). Furthermore, the reference discloses that when a unit of the polymer is exposed to the agent, the interaction between the two produces a signal…if each type of unit e.g., each type of amino acid is labeled with a different light emissive compound having a distinct light emissive pattern then each amino acid will interact with the agent to produce a distinct signal. By

determining what each signal for each unit of the polymer is, the sequence of units can be determined (see column 27, lines 58-67 and column 28, lines 1-5). Furthermore, the reference discloses that the labeled proteins remain completely stationary in space. By direct analogy, the spatial confinement of the nanochannels should limit or eliminate the Brownian motion of the labeled DNA in nanochannel FRET sequencing. This would allow a stable and predictable passage of the DNA through the nanochannels (see column 35, lines 39-64). The instant specification discloses that the skilled artisan will realize that where the specification refers to a “nanopore” different alternatives may use a “nanochannel” or “nanotube”. The only requirement is that the nanopore, nanochannel or nanotube connect one fluid filled compartment to another and allow the passage and detection of labeled protein (see paragraph [0034]). Thus, this reads on claims 1, 7, 10, 11-13 and 16. The reference further teaches a method for analyzing a polymer of linked units comprising moving a plurality of individual units of a polymer of linked units through a channel and exposing the plurality of individual units to an agent selected from the group consisting of electromagnetic radiation, a quenching source and a fluorescence excitation source as the units move past the agent, individual units interacting with the agent to produce a detectable signal within the channel or at the edge of the channel (see Claims 1-4). This further reads on claims 7 and 11-14. The reference teaches that the detected signals can be compared to a known pattern of signals characteristic of a known polymer to determine the relatedness of the polymer being analyzed to the known polymer and analysis may also involve measuring the length of time elapsed between detection of a first signal from the first unit and a second

signal from a second unit. The time elapsed between the sequential detection of signals may indicate the distance between two units or the length of the polymer (see column 8, lines 36-47). Furthermore, the reference teaches that the method involves the steps of causing the polymer to pass linearly relative to a station, detecting a characteristic signal generated as each of the two individual units passes by the station, measuring the time elapsed between the signals measured, repeating steps for a plurality of similar polymers to produce a data set, and determining the distance between the two individual units based upon the information obtained from the plurality of similar polymers by analyzing the data set. Furthermore, the reference teaches that nanochannel can be prepared by electroless deposition procedure which produces a metal fibril running the complete width of the polycarbonate template membrane. The membrane can also be produced such that both faces of the membrane are covered with thin metal films to produce a nanodisk electrode ensemble…This assembly is useful for examining changes in current as polymers flow through changes in conductance can be measured (see column 46, lines 15-20 and 24-26). As evidenced by the instant specification, "the sensor layers may comprise semiconductor material including, but not limited to, silicon, silicon dioxide, silicon nitride, germanium, gallinium arsenide, and/or metal-based compositions such as metals or metal oxides (see paragraph [0078] of instant specification US 2005/0282229 A1). In regards to claim 35, the instant specification does not define what a “sub-nanometer scale" is. Further, since the proteins, polypeptides or peptides are passing though nonochannels, it would inherently have nanometer scales. Furthermore, claim 35 does not further limit the

active method steps of claim 1. Thus, this meets the limitations of claims 1, 4-5, 7-8, 10-14 and 16.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 4-5, 7-8, 10-14, 16 and 35 remain rejected under 35 U.S.C. 102(a) as being anticipated by Chan EY (US Patent # 6355420).

8. The teachings of Chan et al are described, supra.

Response to Applicant's Arguments

9. Applicant argues that "Independent claim 1 recites, inter alia, "passing the labeled proteins, polypeptides or peptides through one or more nanopores, an inner surface of the nanopores coated with a semiconductor material." This feature is not taught by US Patent No. 6,210,896 or US Patent No. 6,355, 420." Applicant argues that "metals, in contrast do not have a band gap. The portion of Example 6 cited by the Examiner clearly states that the polymer of Chan is coated by a metal. The fact that the application of an AC electric field to the applied DC field generates an inhomogenoues field is irrelevant to the materials used. Simply, the application of an electric field to a metal does not change the fundamental properties of the metal or convert the metal into a semiconductor."

10. Applicant's arguments have been fully considered but have not been found persuasive. Both cited references teach all of the active method steps of the instant

claims. Chan ‘896 teaches that polymer is pulled closer to tip using dielectric forces created by applying an AC field to electrode and waveguide, i.e., metal layers, in addition to the DC field applied across wires. The AC field applied capacitively with respect to the DC field generates an inhomogeneous field in nanochannel (see column 36, lines 14-19), meeting the limitation of inner surface of the nanopores coated with a semiconductor material. The active method steps of claim 1 are a) placing a plurality of labeled proteins, polypeptides or peptides in a plurality of chambers, b) passing the labeled proteins, polypeptides or peptides through one or more nanopores, c) detecting labeled amino acid residues in the labeled proteins, polypeptides or peptides, and d) compiling an amino acid distance map for each type of labeled amino acid. Step 2) is a mental process, which does not involve any active method steps. In regards to the inner surface of the nanopores coated with a semiconductor material, this is not an active method step. This is a property of the nanopore, and the "coated" implies that the method step already occurred, and is no longer an active method step. Furthermore, the cited reference (Chan ‘896) teaches that AC field is applied to electrode and waveguide (metal layers) in addition to the DC field applied across wires, and this generates an inhomogeneous field in nannochannel. In regards to Applicant’s argument that “Semiconductors and insulators have a band gap between the valence and conduction bands, with semiconductors having small band gaps relative to insulators. Metal, in contrast do not have a band gap…the application of an electric field to a metal does not change the fundamental properties of the metal or convert the metal into a semiconductor,” all of the elements of the semiconductor is disclosed by Chan '896. The

instant claim recites, "...coated with a semiconductor material." Applicant's specification (published PG Pub 2005/0282229 A1) was utilized to define what a "semiconductor material" is. The instant specification was used to identify what the property of what a semiconductor was. Applicant's specification was not utilized to support Chan '896 reference. Applicant's specification was utilized to explain or define the properties of semiconductor material. As evidenced by the instant specification, "the sensor layers may comprise semiconductor material including, but not limited to, silicon, silicon dioxide, silicon nitride, germanium, gallinium arsenide, and/or metal-based compositions such as metals or metal oxides (see paragraph [0078] of instant specification US 2005/0282229 A1). Therefore, Chan '896 as a whole anticipates all of the active method steps of the claimed invention of instant claims.

Chan patent '420 teaches all of the active method steps of the instant claims. Further, all of the components are disclosed in the Chan reference. Chan '420 also teaches that nanochannel can be prepared by electroless deposition procedure which produces a metal fibril running the complete width of the polycarbonate template membrane. The membrane can also be produced such that both faces of the membrane are covered with thin metal films to produce a nanodisk electrode ensemble…This assembly is useful for examining changes in current as polymers flow through changes in conductance can be measured (see column 46, lines 15-20 and 24-26). Again, the instant claim recites, "...coated with a semiconductor material." Applicant's specification (published PG Pub 2005/0282229 A1) was utilized to define what a "semiconductor material" is. The instant specification was used to identify what

the property of what a semiconductor was. Applicant's specification was not utilized to support Chan '896 reference. Applicant's specification was utilized to explain or define the properties of semiconductor material. As evidenced by the instant specification, "the sensor layers may comprise semiconductor material including, but not limited to, silicon, silicon dioxide, silicon nitride, germanium, gallinium arsenide, and/or metal-based compositions such as metals or metal oxides (see paragraph [0078] of instant specification US 2005/0282229 A1). Therefore, Chan '420 as a whole anticipates the claimed invention of the instant claims.

Rejection-35 U.S.C. 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 3-5, 7-8, 10-14, 16 and 35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chan EY (US Patent # 6210896).

15. The teachings of Chan EY are described supra. The difference between the reference and the instant application is that the reference does not teach obtaining one or more proteins, polypeptides or peptides from a biological sample.

16. However, it would have been obvious to one of ordinary skill in the art to try the method of obtaining the identity of the protein of any sample, including proteins from biological samples, by using the teachings of US Patent '896. There is a reasonable expectation of success since the method and the analysis of the Chan patent works on any polymeric compounds, such as DNA, RNA, and proteins that are labeled with luminescent labels, fluorescent labels, phosphorescent labels, chemiluminescent labels…nuclear magnetic resonance labels…electron spin resonance labels…and are detected with a photodetector or with an electrical detector.

17. Claim 2, 6, 15 and 32-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chan EY (US Patent No. 6,210,896) as applied to claims 1, 3-5, 7-8, 10-14, 16 and 35 above in view of Thompson et al (US Patent No. 5,324,637).

18. The teachings of Chan EY are described supra. The difference between the reference and the instant claims are that the reference does not teach placing nucleic acid into at least one chamber, each chamber containing a different type of labeled amino acid, and producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid, and the amount of labeled amino acid present in each chamber.

19. However, Thompson et al teaches a method for coupling transcription and translation from DNA, wherein RNA is transcribed from DNA and RNA translates into protein (see abstract). The reference further teaches that if a radiolabeled amino acid is used in the coupled reaction, such as ^{35}S methionine or ^{3}H leucine, then the corresponding amino acid is left out of the amino acid mix…RNA polymerase, either SP6, T7 or T3 is then added (see column 8. lines 60-65). Furthermore, the reference teaches that another method of measuring the amount of protein produced in coupled in vitro transcription and translation reactions is to perform the reactions using a known quantity of radiolabeled amino acid such as ^{35}S methionine or ^{3}H leucine and subsequently measuring the amount of radiolabeled amino acid incorporated into the newly translated protein (see column 11, lines 40-46). In regards to claims 32-34, these do not recite active method steps. These method steps are past tense, therefore, the method steps have already occurred. Therefore, when the proteins, polypeptides or

peptides are present, this reads on claims 32-34. Further, it does not matter how the proteins are made, since it is still a protein.

20. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Chan EY patent and Thompson et al patent to obtain the protein identity, because both prior arts teach the identification of proteins, using labeling of the protein such as fluorescence labeling, radiolabeling of proteins (Chan) and radiolabeling of proteins (Thompson) to quantify and identify the proteins. There is a reasonable expectation of success, since Thompson et al provide a simple method for producing protein from a template DNA, such a method which can be used to couple transcription and translation of a single protein coded by the DNA template (see Thompson et al, column 4, lines 13-20). Furthermore, both prior arts teach radiolabeling of proteins to measure the amounts of labeling and Chan teaches limiting the region of detection of the polymer where the radiolabel exists on the protein.

21. It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

22. The "problem" facing those in the art was that sequencing polymer methods are slow and labor intensive. For example, Sanger method involves the enzymatic synthesis of DNA molecules terminating in dideoxynucleotides, and subsequent analysis yields information of the length of the DNA molecules and the nucleotide at which each molecule terminates, and thus, the DNA sequence can be determined. The other method is Maxam and Gilbert method, which uses chemical degradation to generate a population of molecules degraded at certain positions of the target DNA, and with knowledge of the cleavage specificities of the chemical reactions and the lengths of the fragments, the NDA sequence is generated (see Chan patent '896, column 1, lines 32-47) and each process takes about 1-3 days, and there were a limited number of methodologies available to do so, for example radiolabeling the protein sequence, DNA sequencing, mass spectroscopy and ELIDA sequencing. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In this case, Chan patent teaches that any polymer sequence can be labeled and run through the nanochannel, and the distance of each polymeric sequence can be read separately, for any DNA and protein sequences. Thus, performing a transcription coupled translation a radiolabeling the protein that is translated from RNA is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Response to Applicant's Arguments

23. Applicant argues that "Thompson does not teach "passing the labeled proteins, polypeptides or peptide through one or more nanopores, an inner surface of the nanopores coated with a semiconductor material." None of the applied references either singly or in combination teaches or suggests passing the labeled proteins, polypeptides, or peptides through one or more nanopores, an inner surface of the nanopores coated with a semiconductor material as recited in independent claim 1."

24. Applicant's arguments have been fully considered but have not been found persuasive. As described above, Chan reference as a whole teaches the active method steps of instant claims. Chan '896 teaches that polymer is pulled closer to tip using dielectric forces created by applying an AC field to electrode and waveguide, i.e., metal layers, in addition to the DC field applied across wires. The AC field applied capacitively with respect to the DC field generates an inhomogeneous field in nanochannel (see column 36, lines 14-19), meeting the limitation of inner surface of the nanopores coated with a semiconductor material. The active method steps of claim 1 are a) placing a plurality of labeled proteins, polypeptides or peptides in a plurality of chambers, b) passing the labeled proteins, polypeptides or peptides through one or more nanopores, c) detecting labeled amino acid residues in the labeled proteins, polypeptides or peptides, and d) compiling an amino acid distance map for each type of labeled amino acid. Step 2) is a mental process, which does not involve any active method steps. In regards to the inner surface of the nanopores coated with a semiconductor material, this is not an active method step. This is a property of the nanopore, and the "coated"

implies that the method step already occurred, and is no longer an active method step. Furthermore, the cited reference (Chan '896) teaches that AC field is applied to electrode and waveguide (metal layers) in addition to the DC field applied across wires, and this generates an inhomogeneous field in nannochannel. Applicant's specification (published PG Pub 2005/0282229 A1) was utilized to define what a "semiconductor material" is. The instant specification was used to identify what the property of what a semiconductor was. Applicant's specification was not utilized to support Chan '896 reference. Applicant's specification was utilized to explain or define the properties of semiconductor material. As evidenced by the instant specification, "the sensor layers may comprise semiconductor material including, but not limited to, silicon, silicon dioxide, silicon nitride, germanium, gallinium arsenide, and/or metal-based compositions such as metals or metal oxides (see paragraph [0078] of instant specification US 2005/0282229 A1). Therefore, Chan '896 teaches the active method steps and components of the instant claims 1, 3-5, 7-8, 10-14, 16 and 35. However, Chan does not teach nucleic acid into at least one chamber, each chamber containing a different type of labeled amino acid, and producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid, and the amount of labeled amino acid present in each chamber.

Thompson reference teaches that another method of measuring the amount of protein produced in coupled in vitro transcription and translation reactions is to perform the reactions using a known quantity of radiolabeled amino acid such as ^{35}S methionine or ^{3}H leucine and subsequently measuring the amount of radiolabeled amino acid

incorporated into the newly translated protein (see column 11, lines 40-46). Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Chan EY patent and Thompson et al patent to obtain the protein identity, because both prior arts teach the identification of proteins, using labeling of the protein such as fluorescence labeling, radiolabeling of proteins (Chan) and radiolabeling of proteins (Thompson) to quantify and identify the proteins. There is a reasonable expectation of success, since Thompson et al provide a simple method for producing protein from a template DNA, such a method which can be used to couple transcription and translation of a single protein coded by the DNA template. As described in the KSR analysis, sequencing polymer methods are slow and labor intensive, each process taking about 1-3 days, and there were a limited number of methodologies available to do so, for example radiolabeling the protein sequence, DNA sequencing, mass spectroscopy and ELIDA sequencing. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In this case, Chan patent teaches that any polymer sequence or plurality of polymer sequences in multi-well can be labeled and run through the nanochannel, and the distance of each polymeric sequence can be read separately, for any DNA and protein sequences. Thus, performing a transcription coupled translation a radiolabeling the protein that is translated from RNA is a “the product not of innovation but of ordinary skill and common sense,” leading to the conclusion that invention is not patentable as it would have been obvious. Therefore, the prior arts combined are prima facie obvious.

35 U.S.C. 112, 2nd

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 2, 6, 15 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. Claim is recites, "The method of claim 1, further comprising: a) placing a template nucleic acid into each chamber; and b) producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid." It is unclear if the labeled proteins, polypeptides or peptides encoded by the template nucleic acid are same as the labeled proteins, polypeptides or peptides recited in claim 1 or different from those recited in claim 1. Because claims 6 and 15 depend from indefinite claim 2 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Response to Applicant's Arguments

28. Applicant argues that "the embodiment recites in claims 2, 6 and 15 is described in paragraph [0036] of the specification." Applicant argues that "the labeled proteins, polypeptides or peptides encoded by the template nucleic acid of claim 2 could indeed be the same labeled proteins, polypeptides or peptides of claim 1."

29. Applicant's arguments have been fully considered but have not been found persuasive. If the labeled proteins, polypeptide or peptides encoded by the template

nucleic acid of claim 2 could indeed be the same labeled proteins, polypeptide or peptide of claim 1, then the method steps appear to be in incoherent order. Claim 2 recites, “The method of claim1, further comprising a) placing a template nucleic acid into each chamber, and b) producing one or more labeled proteins, polypeptide or peptides encoded by the template nucleic acid." The labeled proteins, polypeptides or peptides already exist in claim 1. Therefore, there is no need to produce one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid in claim 2, since these peptides, polypeptides and proteins already are present in the chamber. Paragraph [0036] discloses that “a nucleic acid template may be placed in one or more chambers, each chamber to contain a different labeled amino acid. Labeled proteins encoded by the nucleic acid template may be produced by in vitro translation or by linked transcription/translation. The labeled proteins may pass through one or more nanopores associated with each chamber.” This implies that the protein must be produced first. However, the order of the claims do not recite this. The claim recites that proteins are placed in the chamber, and can further comprise template nucleic acid in the chambers to produce the labeled proteins. Therefore, the instant claims 2, 6 and 15 are indefinite.

35 U.S.C. 112, 1st

30. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

31. Claims 2, 6, 15 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing labeled nucleic acid from the template nucleic acid, does not reasonably provide enablement for producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention and (5) The breadth of the claims:

The invention is drawn to a comprising: placing plurality of labeled proteins, polypeptides or peptides in a plurality of chambers, such that different chambers contain a different type of labeled amino acid, further comprising placing a template nucleic acid

into each chamber, and producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid.

(2) The state of the prior art:

Branton Lab-Nanopore Sequencing Description (originally filed with IDS, 10/29/2003, however Applicant has not provided copy of this reference) describes characterizing the concentration and size of nucleic acid polymers through a protein channel in a lipid bilayer (see p. 2). Branton Lab further describes that the channel pore can only accommodate one strand of DNA or RNA at a time, and the nanopore behaves as a detector that can rapidly discriminate between pyrimidine and purine segments along single RNA molecules (see p. 2 and Figure 2). Branton Lab describes that this technology can be sued to characterize the sequence of bases in single molecules of DNA (see p. 3).

Su et al (US Patent No. 7,005,264 B2) claims a method comprising a) placing a template nucleic acid into four chambers, each chamber being associated with different nanopores and each chamber comprising a different labeled nucleotide; b) synthesizing a labeled nucleic acid from the template nucleic acid; c) contacting the labeled nucleic acid in each chamber with its associated nanopore, wherein the labeled nucleic acid passes through the associated nanopore; d) detecting a labeled nucleotide; e) compiling a nucleotide distance map for each type of labeled nucleotide; and f) determining the sequence of the nucleic acid from the nucleotide distance maps (see claim 1). Patent

'264 teaches that a labeled nucleic acid can be synthesized from the template nucleic acid.

The art provide guidance as producing labeled nucleic acid from template nucleic acid, characterizing and sequencing polynucleotide, but no art provide guidance as how to produce labeled proteins, polypeptides or peptides of claim 1 from template nucleic acid.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of producing the same labeled proteins, polypeptides or peptides of claim 1 from a template nucleic acid. However, it is unpredictable that a template nucleic acid would produce the same labeled proteins, polypeptides or peptides of claim 1. Since the activity is based on producing the same labeled proteins, polypeptide or peptides of claim 1 from a template nucleic acid, the predictability in the art is low. This is due to the fact that not all template nucleic acid would produce the same labeled proteins, polypeptides or peptide.

As described above, Branton Lab-Nanopore Sequencing Description describes characterizing the concentration and size of nucleic acid polymers through a protein channel in a lipid bilayer (see p. 2). Branton Lab further describes that the channel pore can only accommodate one strand of DNA or RNA at a time, and the nanopore behaves

as a detector that can rapidly discriminate between pyrimidine and purine segments along single RNA molecules (see p. 2 and Figure 2). Branton Lab describes that this technology can be sued to characterize the sequence of bases in single molecules of DNA (see p. 3).

Su et al (US Patent No. 7,005,264 B2) claims a method comprising a) placing a template nucleic acid into four chambers, each chamber being associated with different nanopores and each chamber comprising a different labeled nucleotide; b) synthesizing a labeled nucleic acid from the template nucleic acid; c) contacting the labeled nucleic acid in each chamber with its associated nanopore, wherein the labeled nucleic acid passes through the associated nanopore; d) detecting a labeled nucleotide; e) compiling a nucleotide distance map for each type of labeled nucleotide; and f) determining the sequence of the nucleic acid from the nucleotide distance maps (see claim 1). Patent '264 teaches that a labeled nucleic acid can be synthesized from the template nucleic acid.

The claim doesn't identify the which template nucleic acid, and the claim recites that "a template nucleic acid" and "producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid", therefore, the claim implies that a any one single template nucleic acid would produce the same labeled proteins, polypeptides or peptides of claim 1. However, the Applicant has not shown how a single template nucleic acid would produce the same labeled proteins, polypeptides or peptides of claim 1. There are too many variables between the template nucleic acids

and the proteins, polypeptides or peptides produced from the template nucleic acids, thus, it clearly shows the unpredictability of the art.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The instant specification provides guidance as how to label proteins (see Example 4). For example, methods of labeling proteins on amine residues, such as lysine, arginine and the N-terminal residue of the protein (see paragraph [0126] of instant specification US 2005/0282229 A1). The same Example 4 describes methods of labeling proteins on carboxyl residues, such as glutamate, aspartate and the C-terminal residues (see paragraph [0127] of instant specification as above). The instant specification further discloses Raman detection of analytes, such as single nucleotides, oligonucleotides (see Example 5). Further, the instant specification discloses that "the skilled artisan will realize that the disclosed methods are exemplary only and that the Raman detection techniques disclosed for analysis of nucleotides and oligonucleotides are also applicable for amino acids and proteins" (see paragraph [0145] of instant specification as above, and Example 6).

The specification has not provided guidance in the way of a disclosure as how to produce the same labeled proteins, polypeptides or peptides from a single template of nucleic acid. The specification further does not disclose producing any labeled proteins, polypeptides or peptides from a template nucleic acid. The specification discloses that proteins to be analyzed may be partially or fully purified from a variety of sources before

analysis. The specification lists different well known techniques in the art in protein purification (see paragraphs [0044]-[0048] of instant specification above). The specification further discloses that nucleic acids encoding target proteins of interest may be incorporated into expression vectors fro transformation into host cells and production of the encoded proteins (see paragraphs [0054]-[0063] of instant specification as above).

There is no clear guidance as how to produce the same labeled proteins, polypeptides or peptides from a template nucleic acid, since not all template nucleic acids would encode the same labeled proteins, polypeptides or peptides. Since it is unclear which template nucleic acid would produce the same labeled proteins, polypeptides or peptides, more guidance is necessary.

(8) The quantity of experimentation necessary:

Applicant has not provided how to produce the same labeled proteins, polypeptides or peptides of claim 1 from a template nucleic acid, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study".

Response to Applicant's Arguments

32. Applicant argues that "Paragraph [0036] of the specification explicitly teaches that "labeled proteins encoded by the nucleic acid template may be produced by in vitro translation or by linked transcription/translation." Applicant argues that "the specification

explicitly teaches at least two methods for producing one or more labeled proteins, polypeptides or peptides encoded by the template nucleic acid."

33. Applicant's arguments have been fully considered but not found persuasive. Paragraph [0036] discloses that "a nucleic acid template may be placed in one or more chambers, each chamber to contain a different labeled amino acid. Labeled proteins encoded by the nucleic acid template may be produced by in vitro translation or by linked transcription/translation. The labeled proteins may pass through one or more nanopores associated with each chamber." However the specification does not provide guidance as how to produce labeled proteins from template nucleic acid. The art provide guidance as producing labeled nucleic acid from template nucleic acid, characterizing and sequencing polynucleotide, but no art provide guidance as how to produce labeled proteins, polypeptides or peptides of claim 1 from template nucleic acid. There is no clear guidance as how to produce the same labeled proteins, polypeptides or peptides from a template nucleic acid, since not all template nucleic acids would encode the same labeled proteins, polypeptides or peptides. Since it is unclear which template nucleic acid would produce the same labeled proteins, polypeptides or peptides, more guidance is necessary. Furthermore, Applicant has not provided guidance as how to produce the same labeled proteins, polypeptides or peptides of claim 1 from a template nucleic acid, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study".

New Objection

34. Claim 33 is objected to for the following minor informality: Claim 33 recites, "The method of claim 32, wherein in vitro translation is based on rabbit reticulocytes lysates, wheat germ extracts, or E. *coli* extract" There is a punctuation missing from the claim. Claim 1 is missing a period at the end of the claim. Each claim must end with a period. Applicant is required to correct this error.

New Rejection

35 U.S.C. 112, 2nd

35. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

36. Claims 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

37. Claim 34 recites, "…wherein in vitro translation is based on rabbit reticulocytes lysates, wheat germ extracts, or E. coli extract." It is unclear how an in vitro translation can be based on cells. For example, in vitro translation system can be carried out in these cell systems, but it is unclear how the in vitro translation system can be based on these cells.

38. Claim 35 recites, "…wherein the distance map shows distance in a sub-nanometer scale." It is unclear what "a sub-nanometer scale is The instant specification has not fully defined what "a sub-nanometer scale" is. For example, a micrometer is 10^{-}

^{6}, nanometer is 10^{-9}, a picometer is 10^{-12}, and femtometer is 10^{-15}. However, it is unclear what a sub-nanometer is, since it is not defined. Further, it is unclear if sub-nanometer is less than nanometer or within the nanometer range or close to picometer.

Conclusion

39. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

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